REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 12-16, 18-23 and 25-36 are pending after entry of the amendments set forth herein.

Claims 12-16, 18-23 and 25-30 were rejected. No claims were allowed.

Please replace claims with the clean version provided above.

Claims 12 and 19 are amended and claims 31-36 are added. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claim 12 and 19 and new claims 31-36 may be found in claim 16 as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraph 68 on page 16, and paragraphs 62 and 63, starting on page 12. The claims are amended to recite neuroendocrine bHLH transcription factor, support for which may be found in now cancelled claim 23. The claims are amended to recite insulin-producing cells, support for which may be found in page 33, line 2 Accordingly, no new matter is added by these amendments.

Claim 23 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Drawings

The Examiner has requested a response to the PTO 948 attached to the Office Action.

The PTO 948 indicates that Figs 2A-4B, 6A-6C, 7A, 7B, and 13A-15C are not acceptable until a petition to accept color drawings is granted. However, a petition under 37 CFR §1.84(a)(2), three sets of color photographs, and the appropriate fee set forth in 37 CFR §1.17(h) were filed with the application on March 20, 2001. For the Examiner's convenience, a copy of the petition is enclosed herewith. In this response, Applicants have amended the first paragraph of the brief description of the drawings section of the specification to state the required paragraph.

The Applicants respectfully submit that they have met the requirements of CFR §1.84 and that the petition may be granted.

The PTO 948 indicates that the number and reference characters for Figs. 18A-18C are not plain and legible. Formal Figs. 18A-18C are submitted herewith.

The Response in General

The claims have been rejected for lack of written description and lack of enablement.

The Applicants have adequately described what they are claiming and have provided an enabling disclosure for what they are claiming. Specifically, the Applicants have provided detailed methods for making insulin-producing cells *in vitro* using neuroendocrine class B basic helix-loop-helix (bHLH) transcription factors. Furthermore, the Applicants have provided at least 11 exemplary neuroendocrine class B bHLH transcription factors for use in the subject methods. These exemplary bHLH transcription factors are highly related, and each of them can be grouped into one of three subgroups of class B bHLH proteins based on their phylogenetic relationship: the neurogenins, the neuroD factors, and the mash factors. The Applicants have provided working examples of a representative number of these neuroendocrine class B bHLH transcription factors, one from each of the three bHLH transcription factor subgroups, in methods for making insulin-producing cells. Since a representative number of examples of this genus of neuroendocrine class B bHLH transcription factors are described, and because the use of the described genus of neuroendocrine class B bHLH transcription factors is well within the ability of one of skill in the art using the methods in the specification, the rejections should be withdrawn.

To the extent a further discussion is believed necessary, the Examiner is respectfully referred to the following.

Rejection of claims under 35 USC §112, first paragraph-written description

Claims 12, 18, 19, 20 and 28-30 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in any want as to reasonably convey to one of skill in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. Specifically, the Office Action states that there is no correlation between using neurogenin3 to produce islet cells other than α-cells, and no significant description of a genus of islet transcription factors for producing different types of islet cells. The Applicants respectfully traverse this rejection.

The first part of this rejection appears to question whether there is any evidence that the subject methods can be used to produce islet cells other than α-cells. Since islet cells are well known in the art, as recognized by the Examiner and as described in the specification on, e.g. paragraphs 70-73 on page 14 of the specification, this part of the rejection appears to an enablement rejection. As such, this part of the rejection will addressed in the section entitled "Rejection of claims under 35 USC §112, first paragraph-enablement", below. The question of whether there is an adequate description of a genus of neuroendocrine class b nHLH transcription factors will be addressed below.

The standard for written description has been established over several years of court cases such as *Vas-Cath Inc. v. Mahurkar*[1] and *In re Wertheim*[2] and has culminated in the publication of the "Written Description Guidelines" Federal Register Vol. 66 No. 4, dated January 5, 2001 to which the Office must adhere to when making a written description determination. The law of written description does not require that the specification specifically describe all species that are encompassed by the claims.

A landmark and often cited case involving written description of nucleic acid invention is *Regents of the University of California v. Eli Lilly & Co*[3], hereafter "Lilly". Lilly states that:

> "A description of a genus of cDNAs may be achieved by means of a recitation of **a representative number of cDNAs**, defined by nucleotide sequence, falling within the scope of the genus **or** of a recitation of **structural features** common to the members of the genus."

As such, according to the Law, the written description requirement for a genus of nucleic acids may be satisfied by a) a representative number of species, **or** b) a recitation of structural features common to all members of the species.

The instant specification describes, by explicit reference to their full length sequences, at least 11 exemplary phylogenetically related neuroendocrine class B helix-loop helix transcription factors suitable for use in the subject methods. Fig. 10 of the instant specification, shows the names and phylogenetic relationship between these transcription factors, termed the "neuroendocrine class B bHLH proteins". As can be seen from this figure, the bHLH proteins recited in the subject methods form a clade (i.e. a group

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[1] *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).
[2] *In re Wertheim* 191 U.S.P.Q. 90 (C.C.P.A. 1996)

of sequences that form a branch in a phylogenetic tree) and, as such are all phylogenetically very related to each other, are phylogenetically very different from other class B bHLH proteins, and are phylogenetically very different to other bHLH proteins such as the Class A bHLH proteins. In other words, the sequences of at least 11 exemplary phylogenetically distinct neuroendocrine bHLH transcription factors for use in the subject methods are specifically described in the specification. The Applicants respectfully submit that the sequences of 11 exemplary related neuroendocrine class B bHLH transcription factors for use in the subject methods is an adequate number of neuroendocrine class B bHLH transcription factors to describe the genus of neuroendocrine class B bHLH transcription factors useful in the subject methods. Further, the Applicants respectfully submit that because the 11 exemplary neuroendocrine class B bHLH transcription factors described in the specification are all phylogenetically related, they have also recited a structural feature common to all members of the species. In order to determine whether a class B bHLH transcription factor could be used in the subject claims, one of skill in the art would have to merely have to determine whether it could be phylogenetically grouped with clade of neuroendocrine class B BHLH proteins shown in Fig. 10 of the instant specification.

As such, the Applicants respectfully submit that the specification provides a recitation of a representative number of neuroendocrine class B bHLH transcription factors that are encompassed by the genus of class B bHLH transcription factors for use in the subject methods **and** a recitation of structural features common to all members of that genus. Accordingly, the Applicants respectfully submit that the specification has met the written description requirement for the instant claims.

Applicants respectfully submit that the foregoing discussion overcomes this rejection. The question of whether the described genus of class B bHLH transcription factors is *enabled* for insulin-producing cells is addressed below.

Rejection of claims under 35 USC §112, first paragraph-enablement

Claims 12-13, 18-20 and 25-31 are rejected under 35 USC §112, first paragraph, because the specification, while being enabling for using a nucleic acid encoding neurogenin3 to produce a glucagons producing cell from a cell *in vitro*, assertedly does not reasonably provide enablement for the full scope of the claimed invention. Specifically, the Office Action indicates that described genus of class B bHLH transcription factors is not enabled for making insulin-producing cells. The Office Action further asserts that that because the genus of nucleic acid molecules encoding islet transcription factors

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[3] *Regents of the University of California v. Eli Lilly & Co* 119 F.3d 1559 (Fed. Cir. 1997) at 1568-69

is not supported by a sufficient written description, one of skill in the art would not have know how to make and use the claimed invention so that it would operate as intended. The Office Action further asserts that the claims are not enabled because they do not provide a promoter for the expression of the nucleic acid. The Applicants respectfully traverse this rejection.

The specification is enabling for in vitro methods for making insulin-producing cells

The claims are directed to methods of making insulin-producing cells *in vitro*, and the Office asserts that there is no reasonable correlation provided between *in vivo* and the claimed *in vitro* methods.

The MPEP states at §2164.02:

"An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention..... Since the initial burden is on the examiner to give reasons for the lack of enablement, **the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example**. **A rigorous or an invariable exact correlation is not required**, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)." "..the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. (emphasis added).

The Applicants argue that their *in vivo* results correlate with *in vitro* results.

The Applicants have provided several working examples of making insulin-producing cells *in vivo*. For example, Example 5 on page 38 describes producing insulin in normal adult rats using NGN3 and Example 6 on page 39 describes normalization of glucose levels in diabetic rats using NGN3. The applicants have also provided a detailed description of how to make vectors suitable for use in the subject in vitro methods, and have described, in great detail in paragraphs 122-129 (pages 29-32) how to use the vectors to make insulin-producing cells *in vitro*.

The Office argues that art at the time the application was filed shows that the art was unpredictable. However the evidence that the Office provides articles that merely show that transcription factors for induce beta cell development were not known at the time that the articles were published. It was not until the Applicants discoveries that these factors became known. The articles further do not address whether *in vivo* results correlate with *in vitro* results in this field.

The Applicants respectfully submit that the specification, as filed provides in vivo working examples that correlate with the claimed in vitro methods. The Office has not provided any reasonable

evidence that the in vivo working method *do not* correlate with the claimed in vitro methods. Since the initial burden is on the Office to give reasons for lack of enablement, and the Office has not provided these reasons, the claims should be considered enabled.

Further, in addressing this question, the Applicants refer to a Declaration under 35 C.F.R. § 1.132 by Dr. Michael German.[4] In his declaration, in paragraphs 8 and 9, German states *"The following remarks constitute the basis for my opinion that: Based on the information provided in the '360 patent application, one of skill in the art would expect to be able to successfully perform the claimed in vitro methods of making insulin-producing cells"* and *"In my laboratory, using the methods described in the '360 patent application, we made insulin-producing cells in vitro using the class B bHLH islet transcription factors neurogenin3, neuroD1 and mash1"*. As such, Dr. German has used three neuroendocrine bHLH transcription factors, neurogenin3, neuroD1 and mash1, to make insulin-producing cells *in vitro*. The claims require no more than this to be fully enabled.

The Applicants respectfully submit that they have provided several working examples of *in vivo* methods for making insulin-producing cells and an adequate description of how the claimed *in vitro* methods for making insulin-producing cells may be performed. Based on the foregoing, in combination with Dr. German's Declaration, the Applicants respectfully submit that the claims *in vitro* methods are fully enabled by the specification.

The specification is enabling for the described genus of neuroendocrine class B bHLH transcription factors

Regarding the enablement of a claimed genus, the MPEP states at §2164.02:

"For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation."

As discussed above, the Applicants have described a *genus* of neuroendocrine class B bHLH islet transcription factors that may be used in methods of making insulin-producing cells *in vitro*. The genus of class B bHLH islet transcription factors is represented by a clade of a phylogenetic tree shown in Fig. 10 of the instant specification.

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[4] Applicants note that the law requires the Office to consider this evidence as probative of how one skilled in the art would have viewed the claimed subject matter.

In the working examples of the instant patent application, the Applicants have provided data showing that neurogenin3 may be used to make insulin-producing cells *in vivo*. The Applicants provide herewith a Declaration under 35 C.F.R. § 1.132 by Michael German. In his declaration, Dr. German, in paragraph 9, states "*In my laboratory, using the methods described in the '360 patent application, we made insulin-producing cells in vitro using the class B bHLH islet transcription factors neurogenin3, neuroD1 and mash1.*". Further, in paragraphs 14 and 15 of the Declaration, German states, "*In my opinion, these data are sufficient to show that a number of different types of neuroendocrine class bHLH transcription factors facilitate production of insulin-producing cells in vitro. Neurogenin3, neuroD1 and mash1 are representative of the broader class of neuroendocrine class B bHLH transcription factors exemplified in Fig. 11 of the '360 patent application.*" and "*It is therefore my opinion that one of skill in the art would expect that other members of the class of neuroendocrine class B bHLH transcription factors could be successfully used to produce insulin-producing cells in vitro.*"

The Applicants respectfully submit that neurogenin3, neuroD1 and mash1 are examples that are representative of the genus of class B bHLH transcription factors used in the claimed methods. This is evidenced by the fact that they each grouped into a different subgroup of the neuroendocrine class B bHLH proteins shown in Fig. 10. Neurogenin3, successfully used in the subject methods, is placed in the first subgroup (the neurogenins: ngn3, ngn1 and ngn2), neuroD1 is placed in the second subgroup (the neuroDs: neuroD1, neuroD2, neuroD3 and math2), and mash1 is placed in the third subgroup (the mash factors: mash1 and mas2). Since phylogenetically closely related transcription factors typically have similar functions (see, for example, Lee et al, Curr. Opin. Neurobiol 7:13-20, 1997 and Jan et al, Cell 75: 827-30, enclosed herewith) and the Applicants have provided a single working example of each subgroup of neuroendocrine class B bHLH proteins, one of skill in the art would recognize that the genus of neuroendocrine class B bHLH islet transcription factors could be used in the claimed methods without undue experimentation.

The Applicants respectfully submit that this aspect of the rejection has been adequately addressed.

Finally, the Office stated that the claimed methods were not enabled because there is no promoter used in the methods. The Applicants respectfully submit that the claims, as amended, are enabled with respect to a promoter.

Based on the foregoing, in combination with the Declaration of Dr. German, the Applicants respectfully assert that the specification enables the full scope of the claims. Accordingly, the rejection may be withdrawn.

Rejection of claims under 35 USC §112, second paragraph

Claims 19 and 25 are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action asserts that there is no antecedent basis for the phrase "the islet cell phenotype".

The Applicants respectfully submit that claims 19 and 25, as amended, are not indefinite, and particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Rejection of claims under 35 USC §102 (German)

Claims 12, 18, 19, 20, 28, 29 and 30 are rejected as being anticipated by German (US Patent No. 6,125,598). The Office Action asserts that German teaches methods of producing insulin and/or seratonin in a subject involving transcription factors Nkx-2.2 and Nkx6.1. The Applicants respectfully traverse this rejection.

Nkx-2.2 and Nkx6.1 are not class B bHLH islet transcription factors, and, as such, are not used in the claimed methods. As such, German cannot anticipate the claimed invention.

The Applicants respectfully submit that the foregoing discussion overcomes the rejections. Accordingly, the rejection may be withdrawn.

Rejection of claims under 35 USC §102 (Habener)

Claims 12, 18, 19, 20, 28, 29 and 30 are rejected as being anticipated by Habener (US Patent No. 5,858,973). The Office Action asserts that Habener teaches methods of manipulating the developmental transition of pancreatic α and β cells ex vivo using the transcription factor IDX-1. The Applicants respectfully traverse this rejection.

IDX-1 is not a class B bHLH islet transcription factor, and, as such, are not used in the claimed

methods. As such, Habener cannot anticipate the claimed invention.

The Applicants respectfully submit that the foregoing discussion overcomes the rejections. Accordingly, the rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF-129CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 16, 2003

By: James S Keddie
James S. Keddie, Ph.D.
Registration No. 48,920

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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Attachments: Copy of Petition to Accept Color Drawings or Photographs dated March 20, 2001.
Declaration of Dr. Michael German
Two references: Lee et al, 1997 and Jan et al, 1993.